Proposed Re-evaluation Decision PRVD2016-05

Ferbam

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Overview

What is the Proposed Re-evaluation Decision?

After a re-evaluation of the fungicide ferbam, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing the cancellation of all ferbam uses in Canada.

An evaluation of available scientific information found that, under the current conditions of use, ferbam products pose potential risks of concern to human health and the environment. Based on the health and environmental assessments, risks of concern were identified for both workers and the general public in addition to birds, mammals and aquatic organisms.

This proposal affects all end-use products containing ferbam registered in Canada. This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for ferbam and presents the reasons for the proposed re-evaluation decision.

The information is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides additional technical information on the assessment of ferbam.

PMRA will accept written comments on this proposal up to 60 days from the date of publication of this document. Please forward all comments to Publications (please see contact information indicated on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information.

What is Ferbam?

Ferbam is a protectant fungicide registered in Canada for both food and non-food uses. It is registered to control diseases on tree fruits, berries, grapes, spruce cones, greenhouse vegetables and tobacco (in seedbeds) as a foliar application. Ferbam is applied using ground application equipment by growers, farm workers and professional applicators.

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[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*

Health Considerations

Can Approved Uses of Ferbam Affect Human Health?

Based on the human health risk assessment, all uses of ferbam are proposed for cancellation.

Exposure to ferbam may occur through diet, when handling the product or by entering treated sites. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose at which no effects are observed. Unless there is evidence to the contrary, it is assumed that effects observed in animals are relevant to humans and that humans are more sensitive to effects of a chemical than the most sensitive animal species. For ferbam, toxicology endpoints from a developmental neurotoxicity study in rats were used for risk assessment. Based on the weight of evidence from the available studies, a cancer unit risk value was also established for ferbam.

The risk assessment compares the estimated level of human exposure to the no-effect doses identified in the animal tests. The reference values used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). The estimated exposure to ferbam from domestically produced and imported food commodities exceeded the acute, chronic and cancer reference values established from the toxicology database. Potential risks of concern were identified for workers handling ferbam products during mixing/loading and application as well as from re-entering treated sites following application. Potential risks of concern were also identified from non-occupational exposure following application of ferbam to fruit trees in residential settings.

The ferbam health risk assessment has considered the currently registered use pattern and label directions as well as additional mitigation measures such as additional personal protective equipment, engineering controls to reduce exposure, and modifications to the use pattern (for example, reduced application rates and cancellation of certain uses).

Environmental Considerations

What Happens When Ferbam Is Introduced Into the Environment?

The use of ferbam poses potential risks to birds, mammals and aquatic organisms that cannot be fully mitigated.

Ferbam is not persistent in the environment and breaks down very rapidly to thiram (a registered fungicide) both during and immediately after application. Therefore, the applied active ingredient from ferbam use is expected to be thiram.

Thiram can enter nontarget terrestrial and aquatic habitats through spray drift and can enter aquatic habitats through run-off. Thiram is soluble in water and does not vaporize when sprayed on crops and is not expected to enter the atmosphere and be transported long distances from where it was used. Thiram is nonpersistent in soil and water, breaking down quickly and is not likely to accumulate in fish tissues. Thiram has the potential to move through the soil profile and contaminate groundwater in some types of soil.

When exposed to high enough concentrations, thiram is toxic to birds and mammals, which may be at risk if they consume food sources that have been sprayed with this pesticide. Aquatic organisms are also potentially at risk due to exposure to thiram. The environmental risk assessment considered the currently registered use pattern as well as mitigation in the form of spray buffer zones and label statements highlighting the risk of runoff, however, risks to birds and aquatic organisms cannot be fully mitigated.

Value Considerations

What is the Value of Ferbam?

Ferbam is important for the control of several fungal diseases on apple, stone fruits, berries, grape, greenhouse vegetables, tobacco (seed bed) and spruce cones. It is a contact protectant fungicide with multi-site mode of action. It is used in rotation with single-site fungicides for resistance management, thus prolongs the effective life of these fungicides which are highly prone to the development of resistance.

Proposed Measures to Minimize Risk

Based on the available data and current risk assessments, Health Canada is proposing cancellation of all uses of ferbam. Consequently, all MRLs are proposed for revocation.

Next Steps

The PMRA is inviting stakeholders to submit comments on this document, as well as detailed proposals to further refine the risk assessment and mitigate risks. The PMRA will accept comments and proposals for a period of 60 days from the date of publication of this document. Please forward all comments to Publications.

Before making a final decision on ferbam, the PMRA will consider all comments or proposals received from the public in response to this consultation document. A science-based approach will be applied in making a final decision on ferbam. The PMRA will then publish a re-evaluation decision document, which will include the decision and the reasons for it, a summary of the comments and proposals received on the proposed decision and the PMRA's response to these comments and/or proposals.

If no proposals to refine the risk assessment are received, or if those received are inadequate, then the PMRA will proceed to finalize the re-evaluation decision to cancel all ferbam uses in Canada.

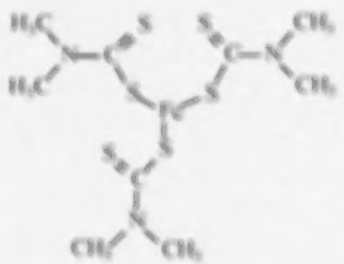
Science Evaluation

1.0 Introduction

Ferbam is a contact, protectant fungicide with multi-site mode of action and belongs to Mode of Action (MoA) group M3. It is registered to control diseases on tree fruits, berries, grapes, spruce cones, greenhouse vegetables and tobacco (in seedbeds) as a foliar spray. Currently, one technical and two commercial end-use products are registered in Canada. Both end-use products are formulated as water-dispersible granules.

2.0 The Technical Grade Active Ingredient, Its Properties and Uses

2.1 Identity of the Technical Grade Active Ingredient.

Common name		Ferbam
Function		Fungicide
Chemical Family		Dithiocarbamate
Chemical name		
1	**International Union of Pure and Applied Chemistry (IUPAC)**	Iron(III) dimethyldithiocarbamate; iron tris (dimethyldithiocarbamate); ferric dimethyldithiocarbamate
2	**Chemical Abstracts Service (CAS)**	(OC-6-11)-tris(dimethylcarbamodithioato-S,S')iron
CAS Registry Number		14484-64-1
Molecular Formula		$C_9H_{18}FeN_3S_6$
Structural Formula		
Molecular Weight		416.5
Purity of the Technical Grade Active Ingredient		87.5 % minimum
Registration Number		30144

2.2 Identity of relevant impurities of human health or environmental concern:

Based on the manufacturing process used, impurities of human health or environmental concern as identified in the Canada Gazette, Part II, Vol. 142, No. 13, SI/2008-67 (2008-06-25), including TSMP Track 1 substances, are not expected to be present in the product.

2.3 Physical and Chemical Properties of the Technical Grade Active Ingredient

Property	Result
Vapour pressure at 25°C	Negligible at 20°C
Ultraviolet (UV)/visible spectrum	Not provided
Solubility in water	130 mg/L (room temperature)
n-Octanol/water partition coefficient	LogP = -4.6
Dissociation constant	Not applicable

2.4 Description of Registered Ferbam Uses

Ferbam is registered in Canada for use on tree fruits (apple, apricot, cherry, peach, pear, plum, and prune), berries (blackberry, boysenberry, cranberry, currant, dewberry, raspberry), grapes, greenhouse vegetables (cucumber, tomato, and lettuce), spruce cones, and tobacco seedbeds. Registered use of ferbam belongs to the following use-site categories: forests and woodlots, greenhouse food crops, terrestrial feed crops, terrestrial food crops and ornamental outdoor

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

The toxicology database for ferbam is incomplete; no guideline studies are available with the exception of acute toxicity studies. Published non-guideline studies were available and were incorporated in the hazard assessment of ferbam. However, these studies were considered inadequate by current standards to adequately characterize potential hazards and select endpoints for risk assessment from dietary and nondietary routes of exposure. Available toxicity and metabolism data were compared with those of thiram and ziram. This process allowed for comparing the toxicological effect levels and endpoints for ferbam with those available for thiram or ziram. Using this data, bridging the toxicity database of ferbam to the database of either ziram or thiram was considered. The United States Environmental Protection Agency and the International Programme on Chemical Safety (IPCS) Joint Meeting on Pesticide Residues (JMPR) have also used this approach to conduct the ferbam risk assessment.

Ferbam was readily absorbed, distributed, extensively metabolized and eliminated primarily in the urine and the expired air of rats following the administration of single oral doses. In pregnant rats, a small amount of the radiolabel metabolite(s) crossed the placenta and was detected in the fetus. In lactating rats, the radiolabel metabolite(s) was secreted into the milk, absorbed by the pups, and eliminated in the urine of the pups.

Overall, available rat metabolism data for thiram, ziram and ferbam indicated that these compounds either rapidly dissociated (ferbam and ziram) or reduced (thiram) into dimethyldithiocarbamate anions and metabolized further to carbon disulfide and dimethylamine. Glucuronide conjugates of dimethyldithiocarbamate and dimethylamine moieties were primarily excreted in the urine while carbon disulfide was excreted solely in the expired air.

Following acute administration, ferbam was of low oral toxicity in rats and low dermal toxicity in rabbits. Ferbam was moderately irritating to the rabbit eyes, nonirritating to the rabbit skin and was a skin sensitizer in guinea pigs. The evidence from the acute studies indicated that thiram, ziram and ferbam have similar acute toxicity profiles.

Systemic effects observed in the animal toxicity studies with thiram and ferbam were similar. These effects included decreased body-weight gain and food consumption starting at 50 mg/kg bw/day for thiram and at 66 mg/kg bw/day for ferbam in the short term dietary studies in rats. In the same studies, congestion of mesenteric lymph node was noted at 50 mg/kg bw/day for thiram and at 109 mg/kg bw/day for ferbam. Thiram and ferbam also resulted in similar lesions in the thyroid and pancreas of rats in the long term dietary studies. These lesions were characterized as squamous metaplasia of thyroid and fatty infiltration of pancreas which were observed starting at 20 mg/kg bw/day for thiram and at 32 mg/kg bw/day for ferbam in the 80-week dietary studies in rats. Further evidence of similarities in the toxicity profile of thiram and ferbam was noted in the reproduction and developmental toxicity studies. For example, in the reproduction toxicity studies in the rat, reduced body-weight gain, food consumption and body weight were observed starting at 4.2 mg/kg bw/day for thiram and at 15 mg/kg bw/day for ferbam. Increased incidences of reduced ossification of sternum, and cleft palate were observed at 12.5 mg/kg bw/day for thiram and at 114 mg/kg bw/day for ferbam in the developmental toxicity studies in the rat. In the same developmental toxicity studies, incidences of hydrocephalus, and cranial malformations were observed at 25 mg/kg bw/day for thiram and at 114 mg/kg bw/day for ferbam.

Overall, in the nonguideline animal toxicity studies with ferbam, effects similar to those produced by thiram were noted, albeit, at higher orally administered doses. The comparison of ferbam and ziram toxicity data revealed that not all these effects were commonly noted in the databases of these two compounds.

Because of the lack of an adequate toxicology database for ferbam, and similarities between toxicity and metabolism of ferbam and thiram, acceptable guideline studies conducted with thiram were used as surrogates to derive endpoints for ferbam risk assessment (Appendix I).

3.2.3 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold to take into account completeness of the data with respect to toxicity to infants and children as well as potential pre- and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

The furfuryl toxicology database was considered inadequate to characterize the potential pre- and postnatal toxicity. While there were some uncertainties in using data bridged from a structural analogue (furan), this concern was attenuated by the high probability that the established effect levels for furan are likely much lower than those predicted for furfuryl. However, because the furfuryl toxicology database was bridged with the furan data, the same concerns identified in the *Pest Control Products Act* hazard consideration of furan are relevant to furfuryl, that is, the *Pest Control Products Act* factor was retained at 10-fold for both acute and repeated exposure scenarios when using the furan developmental neurotoxicity study to establish the point of departure based on neurobehavioural effects in the young and in the absence of maternal toxicity.

3.3 Occupational and Non-Occupational Risk Assessment

3.3.1 Toxicology Endpoint Selection for Occupational and Residential Risk Assessment

Occupational and bystander (all durations, dermal and inhalation routes)

For characterization of occupational and residential, dermal and inhalation, risks for all durations, an oral No Observed Adverse Effect Level (NOAEL) of 1.80 mg/kg bw/day from the furan developmental neurotoxicity study was selected as the most appropriate endpoint. At the Lowest Observed Adverse Effect Level (LOAEL) of 8.30 mg/kg bw/day, reduced body weight, altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze were observed in the young animals in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The *Pest Control Products Act* factor was retained at 10-fold for risk assessments pertaining to residential scenarios. For occupational scenarios, an additional 10-fold factor was applied for protecting any potentially sensitive populations including pregnant workers. Therefore, the target Margin of Exposure (MOE) is 1000-fold for occupational and residential assessments.

Unit Risk for Cancer Assessment

A linear low dose extrapolation (q_1^*) assessment was conducted for thyroid C cell adenomas in females and hepatocellular adenomas in males observed in a 2-year furan dietary study in rats. The calculated q_1^* value for both tumour incidences was 3.5×10^{-2} (mg/kg bw/day)$^{-1}$.

[redacted]

[redacted]

[redacted]

Personal protective equipment (PPE) to be used by occupational handlers are not specified on all ferbam product labels. For the purpose of the M/L/A risk assessment, exposure estimates were determined for workers wearing different levels of PPE (baseline up to full PPE). The use of engineering controls such as closed mixing/loading systems and enclosed cab application equipment was also considered in the risk assessment.

Combined mixer/loader/applicator risks of concern were identified for all groundboom and airblast equipment uses, and for workers using a backpack sprayer for greenhouse applications, even when assuming the highest level of PPE and/or the use of engineering controls. Establishing limits to the amount of ferbam handled (for example, reduced application rate or limits to the area treated per day) were not considered adequate to address potential risk concerns. Exposure to workers mixing/loading and applying ferbam using a manually-pressurized handwand in greenhouses is not of concern provided that single layer PPE and gloves are worn. In addition, mixing/loading for irrigation system application in greenhouses is not of concern provided that that coveralls and gloves are worn and closed mixing/loading systems are used.

3.2.2.2 Postapplication Occupational Exposure and Risk Assessment

The postapplication occupational risk assessment considers exposures to workers who enter treated sites to conduct agronomic activities involving foliar contact (such as handharvesting, thinning, or scouting).

For workers entering treated fields to conduct agronomic activities, dermal exposure is considered to be the primary route of exposure. Considering low volatility of this active ingredient and assuming at least 12 hours have passed before reentry, inhalation exposure to ferbam is not expected for postapplication workers re-entering treated sites.

Postapplication dermal exposure during postapplication activities is expected to be of short-intermediate-term duration for field/orchard crops and long-term duration for greenhouse crops.

Potential exposure of postapplication workers was estimated following a single application at the maximum registered rate using activity-specific transfer coefficients and dislodgeable foliar residue values. The dislodgeable foliar residue refers to the amount of residue that can be dislodged or transferred from a surface, such as leaves of a plant. In the ferbam risk assessment this was assumed to be 25% of the application rate. A transfer coefficient is a measure of the relationship between exposure and the dislodgeable foliar residue for individuals engaged in a specific activity, and is calculated from data generated in field exposure studies (Agricultural Reentry Task Force, ARTF). The transfer coefficients are specific to a given crop and activity combination and reflect standard agricultural work clothing worn by adult workers.

Potential risks of concern were identified for workers reentering treated areas on the day of application for all assessed crop/activity combinations following a single application.

To protect workers involved in postapplication activities, restrictedentry intervals (REIs) were calculated which is the duration of time that must elapse before residues decline to a level where performance of a specific activity results in exposures below the level of concern. Assuming a residue dissipation of 10% per day for field uses, restricted-entry intervals (REIs) of minimum 25 days would be required (0% dissipation assumed for greenhouse uses). The REIs are not expected to be agronomically feasible given need to re-enter fields sooner. Given that potential risks of concern were identified following a single application of ferbam, postapplication risks following multiple applications of this active ingredient have not been assessed.

3.2.3 Residential Handler Exposure and Risk Assessment

There are no residential handler uses of ferbam registered in Canada.

3.2.4 Residential Postapplication Exposure and Risk Assessment

Residential postapplication exposure may occur following application of commercial class ferbam products to fruit trees in residential areas or areas accessible to the general public (for example, residential orchards and gardens). In contrast to professional workers who generally perform one task on one crop throughout the day (for example, harvesting of apples), individuals in residential settings are likely to conduct various activities related to tree maintenance on the same day. Further, the dermal contact is expected to occur as early as on the day of pesticide application and individuals are expected to wear shorts and short-sleeved shirts.

Dermal exposure is considered to be the primary route of postapplication exposure in the residential setting. Considering low volatility of this active ingredient, inhalation exposure to ferbam is not expected for the general public re-entering treated sites.

Dermal exposure estimates for individuals in residential settings conducting postapplication activities related to tree maintenance were calculated using default peak dislodgeable foliar residue values (25% of application rate) for two representative crops (peach and apple) and activity specific transfer coefficients. Lifetime average daily dose values were calculated assuming exposure duration of 1 day per year and a 78-year lifespan.

Potential risks of concern were identified from residential postapplication exposure following application of commercial class ferbam products to fruit trees in residential areas for all population groups (including for children, youths and adults).

3.3 Dietary Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to ferbam from imported foods is also included in the assessment.

These dietary assessments are age-specific and incorporate the different eating habits of the population at various stages of life. Science Policy Notice SPN2003-03, *Assessing Exposure from Pesticides in Food – A User's Guide*, presents detailed acute, chronic and cancer dietary risk assessments procedures used by the PMRA.

The ferbam dietary risk assessment considered exposure from all food sources that could potentially contain ferbam. Residue estimates for ferbam were based on field trial data where available. When field trial data were not available, the Canadian Maximum Residue Limit (MRL) was used to estimate residues in crops. Surveillance data suitable for the purpose of dietary risk evaluation from the Canadian Food Inspection Agency National Chemical Residue Monitoring Program and the United States Department of Agriculture Pesticide Data Program were not available for ferbam. Processing factors, percent of crop treated and food supply information were also used to refine the assessment.

Acute, chronic and cancer dietary risk assessments were conducted using the Dietary Exposure Evaluation Model (Version 2.16) which uses food consumption data from the United States Department of Agriculture's Continuing Surveys of Food Intakes by Individuals, 1994–1996 and 1998.

3.3.1 Toxicology Endpoint Selection for Acute Dietary Risk Assessment

Acute Reference Dose (ARfD)

For characterization of acute dietary risk, the oral NOAEL of 1.86 mg/kg bw/day from the thiram developmental neurotoxicity study was selected as the most appropriate endpoint. At the LOAEL of 4.36 mg/kg bw/day, altered motor activity, decreased motor activity habituation, and effects on learning and memory were observed in the young animals in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. As per the *Pest Control Products Act* section, the *Pest Control Products Act* factor was retained at 10-fold. The composite assessment factor is 1000-fold and is considered protective of any potentially sensitive subpopulations.

$$\text{ARfD} = \frac{\text{1.86 mg/kg bw/day}}{\text{1000}} = \text{0.00186 mg/kg bw}$$

3.3.2 Acute Dietary Exposure and Risk

Acute dietary risk is calculated considering the highest ingestion of ferbam that would be likely on any one day, and using food consumption and food residue values. A statistical analysis compiles all possible combinations of consumption and residue levels to estimate a distribution of the amount that might be consumed in a day. A value representing the high end (99.9th percentile) of this distribution is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects.

The probabilistic assessment results show that based on the current use-pattern the acute dietary (food only) exposure to ferbam (at the 99.9th percentile) results in potential risks of concern for all population subgroups. Several mitigation approaches were explored to decrease the acute dietary exposure (for example, removal of high-residue or high-consumption commodities). Despite the approach taken to limit the dietary exposure, dietary risks of concern remain. Therefore, all registered uses of ferbam are proposed for cancellation and all established MRLs are proposed for revocation.

3.3.3 Toxicology Endpoint Selection for Chronic/Cancer Dietary Risk Assessment

Acceptable Daily Intake (ADI)

To estimate dietary risk from repeated exposure, the oral NOAEL of 1.86 mg/kg bw/day from the thiram developmental neurotoxicity study was selected as the most appropriate endpoint. At the LOAEL of 4.36 mg/kg bw/day, altered motor activity, decreased motor activity habituation, and effects on learning and memory were observed in the young animals in the absence of maternal toxicity. Standard uncertainty factors of 10-fold for interspecies extrapolation and 10-fold for intraspecies variability were applied. The *Pest Control Products Act* factor was retained at 10-fold. The composite assessment factor is 1000-fold and is considered protective of any potentially sensitive subpopulations.

$$\textbf{ADI} = \frac{\textbf{1.86 mg/kg bw/day}}{\textbf{1000}} = \textbf{0.00186 mg/kg bw/day}$$

Unit Risk for Cancer Assessment

A linear low dose extrapolation (q_1^*) assessment was conducted for thyroid C-cell adenomas in females and hepatocellular adenomas in males observed in a 2-year thiram dietary study in rats. The calculated q_1^* value for both tumour incidences was 3.50×10^{-2} $(mg/kg\ bw/day)^{-1}$.

3.3.4 Chronic/Cancer Dietary Exposure and Risk

The chronic dietary exposure was calculated by using the average consumption of different foods and the residue values on those foods. This expected intake of residues was then compared to the ADI for determining chronic risk; or multiplied by the q_1^* to determine the cancer risk.

The chronic assessment results show that based on the current ferbam use pattern the chronic dietary (food only) risk is of concern for all population subgroups. Cancer dietary (food only) risk is also of concern for the general population. As with the acute assessment, several mitigation approaches were explored to decrease the chronic/cancer dietary exposure. Despite this, dietary risks are of concern. Therefore, all registered uses of ferbam are proposed for cancellation and all established MRLs are proposed for revocation.

3.4 Exposure from Drinking Water

3.4.1 Concentrations in Drinking Water

Ferbam is converted almost immediately to thiram, and thus, the transformation product thiram was modelled for drinking water, using application timing for ferbam. Concentrations of thiram in Canadian drinking water sources were modelled using PRZM/EXAMS for surface water and LEACHM for groundwater. The modelling results indicate that thiram (resulting from ferbam use) has the potential to leach into groundwater and runoff to surface water.

It is expected that exposure to ferbam via drinking water would contribute to the overall dietary exposure. However, given the acute/chronic/cancer risks of concern for ferbam from food sources alone, a refined ferbam drinking water exposure and risk assessment has not been conducted at this time.

3.5 Aggregate Risk Assessment

An aggregate exposure and risk assessment for the general public combining the different routes of exposure to ferbam has not been conducted at this time since individual exposure components, for example, residential and dietary exposures result in potential risks of concern individually.

3.6 Human Health Conclusion

The current assessment has considered the currently registered ferbam use pattern and label directions as well as additional mitigation measures such as additional PPE, engineering controls, reduced application rates and removal of certain uses. Potential risks of concern have been identified for most of the assessed human health scenarios (including occupational, residential and dietary scenarios) despite consideration of additional measures to reduce exposure:

- Occupational mixer/loader/applicator risks were identified for all groundboom, airblast and backpack uses.
- Occupational postapplication risks were identified on the day of application for all foliar uses. Required REIs are not expected to be agronomically feasible.
- Residential postapplicationrisks were identified .
- Acute, chronic and cancer dietary exposure (food only) results in potential risks of concern based on the current use pattern.

In most cases, the risks were identified in both the noncancer and cancer risk assessments.

No further refinements to the risk assessment were considered at this time. Given the toxicological properties of ferbam, it is not expected that further refinements to the exposure assessments would change the overall risk conclusions.

4.0 Incident Reports

Since 26 April 2007, registrants have been required by law to report pesticide incidents to the PMRA that are related to their products. In addition, the general public, medical community, government and nongovernmental organizations are able to report pesticide incidents directly to the PMRA. Incidents were searched and reviewed for the active ingredient ferbam. As of 10 June 2015, one human and one domestic animal incident involving this active ingredient (in combination with other active ingredients) have been reported to the PMRA; both occurred in Canada.

The human incident was considered possibly related to the product exposure. The symptoms dizziness and fluttering heart were consistent with the organophosphate (phosalone) component of the product, but not with the known toxicology of ferbam. The domestic animal incident was considered to have at least some degree of association with exposure to the pesticide. Three dogs vomited after ingesting grass treated with a product containing ferbam and phosalone. Both incidents occurred following use in a residential setting. Domestic class products containing ferbam are no longer registered in Canada.

These incident reports were considered in this evaluation and did not affect the risk assessment.

5.0 Value

Ferbam is registered for use as a foliar spray for the control of a number of important fungal diseases on apple, stone fruits (apricot, cherry, peach, plum and prune), berry crops (blackberry, boysenberry, dewberry, raspberry, blueberry, cranberry and currant), greenhouse crops (cucumber, tomato and lettuce), grape, tobacco (seedbed) and spruce cones. It is particularly important for the management of blossom blight and brown rot on apricots, peaches, plums and prunes; coryneum blight on apricots and peaches; leaf curl on peaches and black rot on grapes. Due to its multi-site mode of action and low risk for resistance development, ferbam is used in rotation with other fungicides in an integrated pest management (IPM) program for disease and resistance management.

6.0 Environment

6.1 Fate and Behaviour in the Environment

Ferbam is not a persistent chemical because it transforms rapidly via hydrolysis, phototransformation, and aerobic biotransformation to its major transformation product thiram. The hydrolysis half-life of ferbam is 12 minutes at pH 5, 8 minutes at pH 7 and <0.2 minutes at pH 9. Thus, ferbam is expected to hydrolyze almost completely to thiram in the tank prior to application, and the applied active is expected to be thiram rather than ferbam. As thiram is more persistent in soils and water than ferbam, the following description of the environmental fate and exposure is of thiram rather than ferbam.

Thiram is a soluble chemical (30 mg ai/L) which has a low vapour pressure (2.3 mPa) and it is not expected to volatilize. Thiram degrades rapidly due to phototransformation in soil (half-life 1.2–4.8 days) and in water (half- life 8.8–10.2 hours). Hydrolysis is also an important route of transformation in neutral and alkaline water (half-life 3.5–17.8 days at pH 7 and 6.9 hours–6.9 days at pH 9). However, hydrolysis is much slower in acidic environments (half-life 68.5–169 days at pH 5). Aerobic biotransformation studies indicate that thiram transforms rapidly in soils (DT_{50} 1.4–3.1 days). Thiram also transforms rapidly in aerobic aquatic environments (DT_{50} 1.2–2.2 days) as well as anaerobic aquatic environments (DT_{50} 4.2 days).

The major transformation products of thiram are CO_2 and CS_2, which are both volatile, and so they are not expected to persist in soil or water. Under both aerobic and anaerobic conditions in soil and water, biotransformation of thiram is mainly biphasic, with rapid initial degradation for the first few days, followed by much slower rate of degradation.

Thiram has the potential to leach to groundwater in some types of soil to which it is not tightly bound. The Freundlich K_{ads} values indicate that thiram is immobile or slightly mobile in soils (K_{ads} 54–263). The degree of sorption to soil was not found to be related to the amount of organic matter present, or the soil pH. No leaching studies were available for thiram. In a soil column leaching study of another active (ziram), where thiram was a major transformation product, thiram was not detected in leachate.

No terrestrial field studies are available for Canadian environments or equivalent ecoregions. In terrestrial field studies conducted in California, spray applications of thiram dissipated with half-lives of 27.4 days and 14.4 days for bare ground and turf plots of sandy loam soil, respectively. In North Carolina, the dissipation half-life was 36 days and 62.5 days for a bare ground plot of a sand soil and a turf plot of loamy sand soil, respectively. Dissipation was biphasic in both plots.

6.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on nontarget species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications. Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to nontarget organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative

application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the risk quotient is then compared to the level of concern (LOC). If the screening level risk quotient is below the level of concern, the risk is considered negligible and no further risk characterization is necessary. If the screening level risk quotient is equal to or greater than the level of concern, then a refined risk assessment is performed to further characterize the risk. A refined assessment takes into consideration more realistic exposure scenarios (such as drift to nontarget habitats) and might consider different toxicity endpoints.

Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

6.2.1 Risks to Terrestrial Organisms

For the risk assessment, ferbam toxicity data was not used since ferbam rapidly transforms to thiram. Therefore the applied active is considered to be thiram which is applied at a rate of 0.865 % the ferbam application rate, which takes into account the molecular conversion factor for thiram from ferbam.

Data on avian acute oral or reproductive toxicity of ferbam was not available. Since ferbam transforms rapidly to thiram, the assessment of risk of thiram to terrestrial organisms was based upon an evaluation of toxicity data of thiram to bees, beneficial arthropods, four species of birds and two species of mammals. No data on toxicity to plants were available for review. For the assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following treatment with thiram.

Thiram does not pose a risk to terrestrial invertebrates. The risk assessment showed that the risk from thiram to bees or earthworms was negligible.

Birds and mammals were both found to be at potential risk from consumption of food sources present in-field exposed to thiram the transformation product of ferbam, as well as food sources present off-field exposed to thiram from spray drift. The highest risk for birds and mammals was from reproductive effects with the risk to mammals being mainly to herbivores.

A refined risk assessment was carried out on birds for each of seven crops (plums, peaches, apricots, apples, grapes, cranberries and blueberries. The risk assessment considers both in-field exposure and off-site exposure, as well as using a default half-life for thiram on vegetation of 10 days, and the use of mean nomogram residues to calculate the estimated daily exposure. Many of the acute oral, dietary and reproductive risk quotients exceeded the LOC for in-field exposures for birds. Risk quotients were particularly large for the reproductive risk to small and medium sized insectivores and large herbivores. The largest on-field risk quotient was 712.6 for small insectivores (reproduction) following application to peaches. Off-field exposure resulting from spray drift also exceeded the LOC by a wide margin for reproductive effects at all of the

application rates. The largest off-field risk quotient was 527.3 for small insectivores (reproduction) following applications to peaches. For the risk quotients that exceed the LOC, the percentage of the diet required to reach the LOC ranged from 0.1% for small insectivorous birds (reproductive effects, peaches) up to 100% of the diet to reach the LOC. 0.1% of the diet contaminated with ferbam is equivalent to 0.6 minutes of feeding on contaminated food to reach the LOC. These risks to birds cannot be fully mitigated.

For mammals, a refined risk assessment was carried out using a default half-life for thiram on vegetation of 10 days, as well as the use of mean nomogram residues to calculate the exposure. Many of the acute oral and reproductive risk quotients still exceeded the LOC for in-field exposures and there were many exceedances of the LOC for off-site (spray drift) exposures as well, particularly at the higher application rates. The largest exceedances occurred with herbivores for reproductive effects. The highest on-field risk quotient was 40.8 for a medium sized herbivore consuming short grass following application to peaches.

For the risk quotients exceeding the LOC for mammals, the percentage of the diet required to reach the LOC for acute oral and reproductive effects ranged from 2.5% (reproduction, medium sized herbivores consuming leafy foliage) to 99% of the diet. 2.5% of the diet contaminated with ferbam is equivalent to 36 minutes of feeding on contaminated food to reach the LOC. These risks to mammals cannot be fully mitigated.

6.2.2 Risks to Aquatic Organisms

As ferbam hydrolyzes very rapidly (within minutes) to thiram in water and as this is expected to occur in the spray tank, the potential exposure to aquatic organisms would be from thiram. Thus, for the risk assessment, thiram toxicity data was used. The resulting application rate of thiram is 0.865 % the ferbam application rate.

Available toxicity data on thiram consisted of eight freshwater species (one invertebrate, five fish, and two algae) and three estuarine/marine species (two invertebrates and one fish).There was no chronic toxicity data available for estuarine/marine invertebrates or fish.

At the screening level, risk quotients for freshwater invertebrates exceeded the acute and chronic LOC's by a wide margin for direct application and for spray drift. A refined risk assessment using PRZM/EXAMS modeling data for runoff indicated that the LOC's were still exceeded for Quebec peach and plum scenarios.

At the screening level, risk quotients for freshwater fish exceeded the acute and chronic LOC's by a wide margin both for direct application to water as well as for spray drift. A refined risk assessment using PRZM/EXAMS modeling data for runoff indicated that the LOC's were still exceeded for Quebec peach and plum scenarios.

For amphibians, the thiram toxicity data for freshwater fish were used as a surrogate for amphibians in the risk assessment (for example, LC_{50} 0.042 mg ai/L for Bluegill sunfish, and chronic NOEC 0.00032 mg ai/L for rainbow trout). At the screening level, risk quotients for amphibians exceeded the acute and chronic LOC's by a very large margin for direct application to water and for spray drift. A refined risk assessment for runoff indicated that the LOC's were still exceeded.

At the screening level, risk quotients for freshwater algae exceeded the LOC for direct application and for spray drift. A refined risk assessment for runoff indicated that the risk quotients did not exceed the LOC.

At the screening level, acute risk quotients for estuarine/marine invertebrates and fish exceeded the LOC for direct application and for spray drift. A refined risk assessment using PRZM/EXAMS modeling data for runoff indicated that the LOC was not exceeded for runoff.

6.3 Environmental Conclusion

As ferbam transforms rapidly to thiram in water, the risk assessment was conducted on thiram. Thiram presents significant risks to certain terrestrial organisms (mammals and birds) from consuming food sources contaminated by direct application as well as sites contaminated by spray drift. Risks posed to birds and mammals cannot be fully mitigated. Thiram also presents risks to some aquatic organisms from runoff and spray drift.

7.0 Pest Control Product Policy Considerations

7.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, those that meet all four criteria outlined in the policy, for example, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, ferbam and its transformation product thiram were assessed in accordance with the PMRA Regulatory Directive DIR99-03[2] and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

Ferbam and its transformation product thiram do not meet Track 1 criteria, and do not form any transformation products which meet the Track 1 criteria.

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2 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*.

7.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical are compared against the list in the *Canada Gazette*. The list is used as described in the PMRA Notice of Intent NOE2005-01[3] and is based on existing policies and regulations including DIR99-03 and DIR2006-02[4], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade Ferbam does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through PMRA formulant initiatives and Regulatory Directive DIR2006-02 (PMRA Formulants Policy).

8.0 Proposed Regulatory Decision

After a re-evaluation of ferbam, Health Canada's PMRA, under the authority of the *Pest Control Products Act*, is proposing cancellation of all ferbam uses in Canada. Furthermore, all established maximum residue limits (MRLs) for ferbam are proposed for revocation.

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3 NOE2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the New Pest Control Products Act.

4 DIR2006-02, *Formulants Policy and Implementation Guidance Document*.

List of Abbreviations

ADI	Acceptable Daily Intake
AHETF	Agricultural Handlers Exposure Task Force
ARfD	Acute Reference Dose
ARTF	Agricultural Re-entry Task Force
ATPD	Area treated per day
CAF	Composite Assessment Factor
IPCS	International Programme on Chemical Safety
JMPR	Joint Meeting on Pesticide Residues
LOAEL	Lowest Observed Adverse Effect Level
MoA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
NOAEL	No Observed Adverse Effect Level
PCPA	Pest Control Products Act
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PPE	Personal protective equipment
REI	Restricted-Entry Interval
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
WDG	Water dispersible granule

Appendix 1 Toxicology Endpoints for Health Risk Assessment for Fenthion

	[illegible] (mg/kg bw/day)	[illegible] (as [illegible])	[illegible] and [illegible][1]
[illegible] (All Populations)	[illegible]	NOAEL = [illegible] mg/kg bw/day [illegible] (Altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze)	[illegible] = [illegible] [illegible] = [illegible]
[illegible] (All Populations)	[illegible]	NOAEL = [illegible] mg/kg bw/day [illegible] (Altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze)	[illegible] = [illegible] [illegible] = [illegible]
[illegible] (All durations and all routes)		NOAEL = [illegible] mg/kg bw/day [illegible] (Altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze)	[illegible] = [illegible] [illegible] = [illegible]
[illegible] (All durations and all routes)		NOAEL = [illegible] mg/kg bw/day [illegible] (Reduced body weight, altered motor activity, decreased motor activity habituation, and increase in time taken to complete the Morris maze)	[illegible] = [illegible]
[illegible]	$q_1^* = [illegible]$ (mg/kg bw/day)$^{-1}$	Based on thyroid C cell adenomas in females and hepatocellular adenomas in males	

[1] [illegible] is composite assessment factor; refer to the text of assessment; and [illegible] = [illegible]; [illegible] = [illegible]; [illegible] = [illegible];

Appendix II Toxicity to Nontarget Species

Organism	Study type	Species	Test material	Endpoint	Value* (effect)	Effect of concern	Reference
Terrestrial Species							
Invertebrate	Acute contact	Honey bee (*Apis mellifera*)	Ferbam	48 h LD_{50}	**73.02 µg ai /bee**	Mortality	PMRA
			Thiram	48 h LD_{50}	>7.9 µg ai /bee	Mortality	PMRA 1752918
	Acute contact	Earthworm (*Eisenia foetida*)	Ferbam	LD_{50}	No data		PMRA
			Thiram	LD_{50}	**5.80 g ai/ha**	Mortality	PMRA 1830692
Birds			Ferbam		No data		
	Acute oral	Mallard (*Anas platyrhynchos*)	Thiram	LD_{50}	> 2800 mg ai/kg bw	Mortality	PMRA 1752918
		Ring Necked Pheasant (*Phasianus colchicus*)		LD_{50}	**67.3 mg ai/kg bw**	Mortality	PMRA 1752918
		Red-winged blackbird (*Agelaius phoeniceus*)		LD_{50}	> 100 mg ai/kg bw	Mortality	PMRA 1752918
		Starling (*Sturnus vulgatis*)		LD_{50}	> 100 mg ai/kg bw	Mortality	PMRA 1752918
	Dietary	Bobwhite Quail (*Coturnix virginianus*)	Thiram	LC_{50}	**3950 mg ai/kg diet**	Mortality	PMRA 1752918
		Mallard (*Anas platyrhynchos*)		LC_{50}	5000 mg ai/kg diet	Mortality	PMRA 1752918
		Ring Necked Pheasant (*Phasianus colchicus*)		LC_{50}	>5000 mg ai/kg diet	Mortality	PMRA 1752918
		Japanese quail (*Coturnix c. japonia*)		LC_{50}	>5000 mg ai/kg diet	Mortality	PMRA 1752918
	Reproduction	Bobwhite Quail (*Coturnix virginianus*)	Thiram	NOEC	500 mg ai/kg diet	Mortality	PMRA 1752918 & 1830692
		Mallard (*Anas platyrhynchos*)		NOEC	**9.6 mg ai/kg diet**	Mortality	PMRA 1752918
		Mallard (*Anas platyrhynchos*)		NOEC	<50 mg ai/kg diet	Mortality	PMRA 1752918

Mammals			Ferbam		No data		
	Acute oral	Rat	Thiram	LD_{50}	2600 mg ai/kg bw	Mortality	PMRA 1752918
			Thiram	LD_{50}	**620 mg ai/kg bw**	Mortality	Data from Health Evaluation Directorate
	Reproduction	Rat	Thiram	NOEL	**11 mg ai/kg bw /day**	Reproduction	Data from Health Evaluation Directorate
Aquatic Species							
Freshwater Invertebrates			Ferbam		No data		
	Acute	*Daphnia magna*	Thiram	48-h LC_{50}	**0.011 mg a.i./L**	Immobility	PMRA 1752918 & or 1830692
	Acute	*Daphnia magna*	Thiram	48-h EC_{50}	0.21 mg a.i./L	Immobility	PMRA 1752918 & or 1830692
	Chronic	*Daphnia magna*	Thiram	21 d NOEC	**0.001mg ai /L**	Growth and reproduction	PMRA 1752918 & or 1830692
Estuarine/ marine Invertebrates	Acute	Eastern oyster (*Crassostrea gigas*)	Ferbam	LC_{50}	0.077 mg a.i./L	Mortality	PMRA
	Acute	Mysid shrimp (*Mysidopsis bahia*)	Thiram	96-h LC_{50}	**0.0036 mg a.i./L**	Mortality	PMRA 1752918 & or 1830692
		Eastern oyster (*Crassostrea gigas*)		96-h EC_{50}	0.0047 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
	Chronic		Thiram		No data		
Freshwater Fish	Acute	Carp (*Cyprinus carpio*)	Ferbam	96-h LC_{50}	0.09 mg a.i./L	Mortality	PMRA
		Fathead minnow (*Pimephales promelas*)		96-h LC_{50}	3.0 mg a.i./L	Mortality	PMRA
		Channel catfish		96-h LC_{50}	12.6 mg a.i./L	Mortality	PMRA
		Juvenile Longnose killifish		96-h LC_{50}	1.0 mg a.i./L	Mortality	PMRA

		Rainbow trout (*Oncorhynchus mykiss*)	Thiram	96-h LC_{50}	0.50 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.13 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.28 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
		Bluegill sunfish (*Lepomis macrochirus*)	Thiram	96-h LC_{50}	**0.042 mg a.i./L**	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.28 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
				96-h LC_{50}	0.13 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
		Fathead minnow (*Pimephales promelas*)	Thiram	96-h LC_{50}	0.27 mg a.i./L	Mortality	PMRA 1752918 & or 1830692
	Chronic (Early Life Stage)	Rainbow trout (*Oncorhynchus mykiss*)	Thiram	60-d NOEC	**0.00032 mg ai/L**	Mortality	PMRA 1752918 & or 1830692
Estuartine/ marine Fish			Ferbam		No data		
	Acute	Sheepshead minnows (*Cyprinodon variegatus*)	Thiram	96-h LC_{50}	**0.54 mg ai/L**	Mortality	PMRA 1752918 & or 1830692
	Chronic		Ferbam/ thiram		No data		
Freshwater Plants & Algae	Acute	Algae (*Chlorella pyrenoido*)	Thiram	96 h EC_{50}	1.0 mg ai/L	Biomass	PMRA 1752918 & or 1830692
		Green alga (*Selenastrum capricornutum*)	Thiram	48 h EC_{50}	**0.14 mg ai/L**	Biomass	PMRA 1752918 & or 1830692
		Duckweed (*Lemna gibba*)	Thiram	96 h EC_{50}	1.6 mg ai/L	Biomass	PMRA 1752918 & or 1830692
* Values Used In Risk Assessment Highlighted In Bold Font							

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